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Coronary calcium score scans for attenuation correction of quantitative PET/CT (13)N-ammonia myocardial perfusion imaging

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Abstract: **PURPOSE:** The aim of this study was to evaluate whether ECG-triggered coronary calcium scoring (CCS) scans can be used for attenuation correction (AC) to quantify myocardial blood flow (MBF) and coronary flow reserve (CFR) assessed by PET/CT with (13)N-ammonia. **METHODS:** Thirty-five consecutive patients underwent a (13)N-ammonia PET/CT scan at rest and during standard adenosine stress. MBF values were calculated using AC maps obtained from the ECG-triggered CCS scan during inspiration and validated against MBF values calculated using standard non-gated transmission scans for AC. CFR was calculated as the ratio of hyperaemic over resting MBF. In all 35 consecutive patients intraobserver variability was assessed by blinded repeat analysis for both AC methods. **RESULTS:** There was an excellent correlation between CT AC and CCS for global MBF values at rest ($n = 35$, $r = 0.94$, $p < 0.001$) and during stress ($n = 35$, $r = 0.97$, $p < 0.001$) with narrow Bland-Altman (BA) limits of agreement (-0.21 to 0.10 ml/min per g and -0.41 to 0.30 ml/min per g) as well as for global CFR ($n = 35$, $r = 0.96$, $p < 0.001$, BA -0.27 to 0.34). The excellent correlation was preserved on the segmental MBF analysis for both rest and stress ($n = 1190$, $r = 0.93$, $p < 0.001$, BA -0.60 to 0.50) and for CFR ($n = 595$, $r = 0.87$, $p < 0.001$, BA -0.71 to 0.74). In addition, reproducibility proved excellent for global CFR by CT AC ($n = 35$, $r = 0.91$, $p < 0.001$, BA -0.42-0.58) and CCS scans ($n = 35$, $r = 0.94$, $p < 0.001$, BA -0.34-0.45). **CONCLUSION:** Use of attenuation maps from CCS scans allows accurate quantitative MBF and CFR assessment with (13)N-ammonia PET/CT.

DOI: <https://doi.org/10.1007/s00259-009-1271-1>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-23238>

Journal Article

Published Version

Originally published at:

Burkhard, N; Herzog, B A; Husmann, L; Pazhenkotttil, A P; Burger, I A; Buechel, R R; Valenta, I; Wyss, C A; Kaufmann, P A (2010). Coronary calcium score scans for attenuation correction of quantitative PET/CT (13)N-ammonia myocardial perfusion imaging. *European Journal of Nuclear Medicine and Molecular Imaging*, 37(3):517-521.

DOI: <https://doi.org/10.1007/s00259-009-1271-1>

Coronary calcium score scans for attenuation correction of quantitative PET/CT ^{13}N -ammonia myocardial perfusion imaging

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Received: 8 May 2009 / Accepted: 24 August 2009 / Published online: 23 September 2009
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Abstract

Purpose The aim of this study was to evaluate whether ECG-triggered coronary calcium scoring (CCS) scans can be used for attenuation correction (AC) to quantify myocardial blood flow (MBF) and coronary flow reserve (CFR) assessed by PET/CT with ^{13}N -ammonia.

Methods Thirty-five consecutive patients underwent a ^{13}N -ammonia PET/CT scan at rest and during standard adenosine stress. MBF values were calculated using AC maps obtained from the ECG-triggered CCS scan during inspiration and validated against MBF values calculated using standard non-gated transmission scans for AC. CFR was calculated as the ratio of hyperaemic over resting MBF. In all 35 consecutive patients intraobserver variability was assessed by blinded repeat analysis for both AC methods. **Results** There was an excellent correlation between CT AC and CCS for global MBF values at rest ($n=35$, $r=0.94$, $p<0.001$) and during stress ($n=35$, $r=0.97$, $p<0.001$) with narrow Bland-Altman (BA) limits of agreement (-0.21 to 0.10 ml/min per g and -0.41 to 0.30 ml/min per g) as well as for global CFR ($n=35$, $r=0.96$, $p<0.001$, BA -0.27 to 0.34). The excellent correlation was preserved on the

segmental MBF analysis for both rest and stress ($n=1190$, $r=0.93$, $p<0.001$, BA -0.60 to 0.50) and for CFR ($n=595$, $r=0.87$, $p<0.001$, BA -0.71 to 0.74). In addition, reproducibility proved excellent for global CFR by CT AC ($n=35$, $r=0.91$, $p<0.001$, BA -0.42 – 0.58) and CCS scans ($n=35$, $r=0.94$, $p<0.001$, BA -0.34 – 0.45).

Conclusion Use of attenuation maps from CCS scans allows accurate quantitative MBF and CFR assessment with ^{13}N -ammonia PET/CT.

Keywords Attenuation correction · Coronary calcium score · PET · Myocardial blood flow

Introduction

PET is currently the accepted gold standard for non-invasive myocardial perfusion imaging (MPI) in patients with suspected or known coronary artery disease (CAD). The main advantage of PET over SPECT is its superior spatial resolution and the possibility of non-invasive quantification of the regional myocardial blood flow (MBF) if appropriate tracers [1–5] and adequate attenuation correction (AC) are used. CT images can be transformed into PET attenuation coefficients which allow correction for myocardial perfusion quantification using a hybrid PET/CT scanner [6, 7]. In view of the growing importance of coronary calcium scoring (CCS) for the non-invasive assessment of CAD and the increasing availability of hybrid PET/CT devices, it appears pertinent to evaluate whether multislice CT data from a CCS scan obtained on a hybrid scanner can be used for reliable AC of quantitative MBF from PET/CT and ^{13}N -ammonia, similar to previous validation for qualitative SPECT MPI [8].

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Therefore, the aim of this study was to evaluate whether ECG-triggered CCS scans can be used for AC to quantify MBF and coronary flow reserve (CFR) assessed by PET/CT with ^{13}N -ammonia.

Methods

Study population

We included 35 consecutive patients (7 women, 28 men) referred for assessment of ischaemic heart disease with ^{13}N -ammonia MPI. The mean age was 65 ± 8.5 years (range: 48–84 years) and mean body mass index was $28.4 \pm 5.6 \text{ kg/m}^2$ (range: 17.1–47.9 kg/m^2). Thirty participants had angiographically documented CAD and a history of percutaneous coronary revascularization ($n=12$), myocardial infarction ($n=19$) or previous coronary artery bypass grafting ($n=12$). Five patients were evaluated for microvascular disease. The study was approved by the local Institutional Review Board and written informed consent was obtained from the study participants.

PET and CT imaging

MBF was assessed at rest and during standard adenosine stress (0.14 mg/min per kg of body weight) [9]. Blood pressure and heart rate were recorded every minute and the electrocardiogram was monitored continuously throughout the procedure. Images were acquired either on a Discovery RX (16-slice CT) or a DVCT (64-slice CT) (GE Healthcare). First, a CT scout scan was used to localize the field of view for the following CT and emission scans. Transmission data for CT AC were acquired in a non-gated low-dose CT scan, using the following parameters: scan length 15 cm, rotation time 0.5 s (16-slice CT) or 0.35 (64-slice CT), tube voltage 140 kV, body contour-adapted modulation of tube current (30–120 mA) and slice thickness 3.75 mm. CCS scans were performed during inspiration with prospective ECG triggering using the following parameters: 15 cm, 0.5 s (16-slice CT) or 0.35 (64-slice CT), 140 kV, tube current 400 mA and 2.5 mm. All patients received 750–1,000 MBq ^{13}N -ammonia into a peripheral vein during 10 s as a slow bolus. Dynamic 3-D PET acquisition was started in parallel and consisted of nine 10-s, six 15-s, three 20-s, two 30-s and one 120-s frames as previously reported [4]. PET data were reconstructed using a standard filtered backprojection algorithm with an 8-mm Hanning filter and standard decay scatter sensitivity corrections (voxel size 2.34, 2.34, 3.27). AC was separately performed with CT AC and CCS scans. Quality control included check for misalignment between emission and transmission before reconstruction of PET row data with coregistered CT or CCS scan.

Image processing and MBF

MBF was determined in all patients using the PCARD module of the PMOD software package (version 2.95, PMOD Technologies Ltd, Zurich, Switzerland) [10–12]. In summary, quantification consisted of the following semi-automatic processing steps: (1) reorientation of the images into short axis orientation, (2) definition of volumes of interest in the blood pool of the left (LV) and right ventricle (RV) and (3) a 17-segment model of the LV myocardium was used as previously suggested [13]. Average time-activity curves (TAC) were assessed in the LV, the RV and in each of the 17 myocardial segments [5]. Fitting of a one-tissue compartment model included metabolite correction to the first 4 min of the myocardial TACs as well as to the TAC comprising the signal from all segments (average global flow). In addition to the kinetic parameters the model includes factors for geometrical spillover [14] from LV and RV, which were also fitted. The fits resulted in MBF values with units of ml/min per g of myocardial tissue. CFR was calculated as the ratio of hyperaemic over resting MBF (relative value) [15]. Segmental results were further grouped into the three main coronary territories (left anterior descending, LAD; circumflex artery, CX; and right coronary artery, RCA).

Statistical analysis

The MBF values at rest and during stress are expressed as mean \pm standard deviation (SD). Comparison of mean MBF and CFR values obtained by CT AC and CCS scan was performed using the paired *t* test. Linear regression analysis (Pearson's correlation coefficient) and Bland-Altman (BA) limits of agreement [16] were used to compare individual values. A *p* value <0.05 was considered statistically significant. To assess the intraobserver reproducibility of CT AC as well as CCS scan we blindly reanalysed all ^{13}N -ammonia PET/CT scans 1 month apart including realignment of PET and CT. All statistical analyses were performed using a commercially available SPSS software package (SPSS 15.0, SPSS Inc., Chicago IL, USA).

Results

Intraobserver variability proved excellent for both CT AC and CCS for global and segmental MBF (rest and stress) and CFR values (Table 1).

Global MBF values by CCS scan and CT AC compared well at rest (0.96 ± 0.21 vs 1.02 ± 0.23 ml/min per g, *p* = ns) and during stress (1.7 ± 0.66 vs 1.76 ± 0.70 ml/min per g, *p* = ns), resulting in similar global CFR (1.77 ± 0.59 vs 1.75 ± 0.60 , *p* = ns) without significant differences document-

Table 1 Intraobserver variability of MBF and CFR

Table 1 Intraobserver variability of MBF and CFR		CT AC			CCS		
		<i>r</i>	<i>p</i>	BA	<i>r</i>	<i>p</i>	BA
	Global						
<i>MBF</i> myocardial blood flow (ml/min per g), <i>CFR</i> coronary flow reserve (relative units), <i>CT</i> <i>AC</i> computed tomography attenuation correction, <i>CCS</i> coronary calcium score scan, <i>r</i> correlation coefficient, <i>BA</i> Bland-Altman limits of agreement	MBF rest (<i>n</i> =35)	0.80	<0.001	−0.32–0.23	0.92	<0.001	−0.26–0.24
	MBF stress	0.92	<0.001	−0.54–0.49	0.95	<0.001	−0.46–0.44
	CFR	0.91	<0.001	−0.42–0.58	0.94	<0.001	−0.34–0.45
	Segmental						
	MBF rest (<i>n</i> =595)	0.80	<0.001	−0.52–0.53	0.80	<0.001	−0.42–0.46
	MBF stress	0.83	<0.001	−0.87–0.87	0.92	<0.001	−0.59–0.60
	CFR	0.80	<0.001	1.02 −1.04	0.86	<0.001	−0.73–0.68

ing an excellent correlation with narrow BA limits of agreement (Table 2). The correlation of global MBF values from both AC methods holds true over a wide range of resting and hyperaemic MBF values ($n=70$, $r=0.98$, $p = \text{ns}$, BA −0.33 to 0.21 ml/min per g) as reflected by the excellent correlation of global CFR ($n=35$, $r=0.96$, $p = \text{ns}$, BA −0.27 to 0.34) (Fig. 1). The excellent correlation was preserved for segmental MBF ($n=1,190$, $r=0.93$, $p<0.001$, BA −0.60 to 0.50) and CFR ($n=595$, $r=0.87$, BA −0.71 to 0.74). Correlation was equally maintained for MBF and CFR after grouping segmental values into the main coronary territories (Table 3). The mean global CCS was $1,093\pm 832$ (Agatston units) with separate mean values of 555 ± 386 for LAD, 138 ± 164 for CX and 400 ± 470 for RCA.

Discussion

In the present study we have investigated whether the use of CCS scans for AC of quantitative MPI with ^{13}N -ammonia PET/CT is feasible. Global and regional MBF and CFR measurements obtained by CCS scan provided results highly comparable to those obtained with conventional CT AC. In addition, this holds true for each of the three coronary vessels underlining the clinical validity. Because of its ability to provide non-invasive regional absolute quantification of MBF [5], MPI with ^{13}N -ammonia PET/CT has been often used as a standard of reference to assess CFR in healthy volunteers and in cardiac patients.

The novelty of the present study is that MPI with PET/CT can provide CCS values on top of quantitative MPI without additional need for an unenhanced CT scan for AC, as the latter can be performed with a CCS scan. The agreement of the quantitative MBF and CFR values for CT AC and CCS and the intraobserver reproducibility observed in our study lies well within the range reported in previous studies using various types of stress such as adenosine [17], bicycle stress [12], dobutamine [18] or cold pressor test [11, 19] and different reconstruction algorithms [20] or tracers [3]. This further strengthens the validity of our results supporting the notion that CCS scans can be used for AC of quantitative MBF assessment by PET MPI. This has clinical implications, because CCS has been established as a valuable diagnostic indicator and highly prognostic predictor of cardiovascular events [21]. Recently, CCS has emerged as an important adjunct to SPECT [4] or PET [22] MPI providing diagnostic and prognostic information. In particular, in patients with normal perfusion, some authors have found an added value of high calcium score to discriminate between low and high event rate [22] or to identify CAD [23]. This may mainly apply to patients with intermediate likelihood for CAD, whereas our population may represent a slightly higher likelihood of CAD as a history of CAD was not uncommon. However, the scope of the present study was to prove the validity of AC by CCS in unselected patients, and known CAD was not an exclusion criterion.

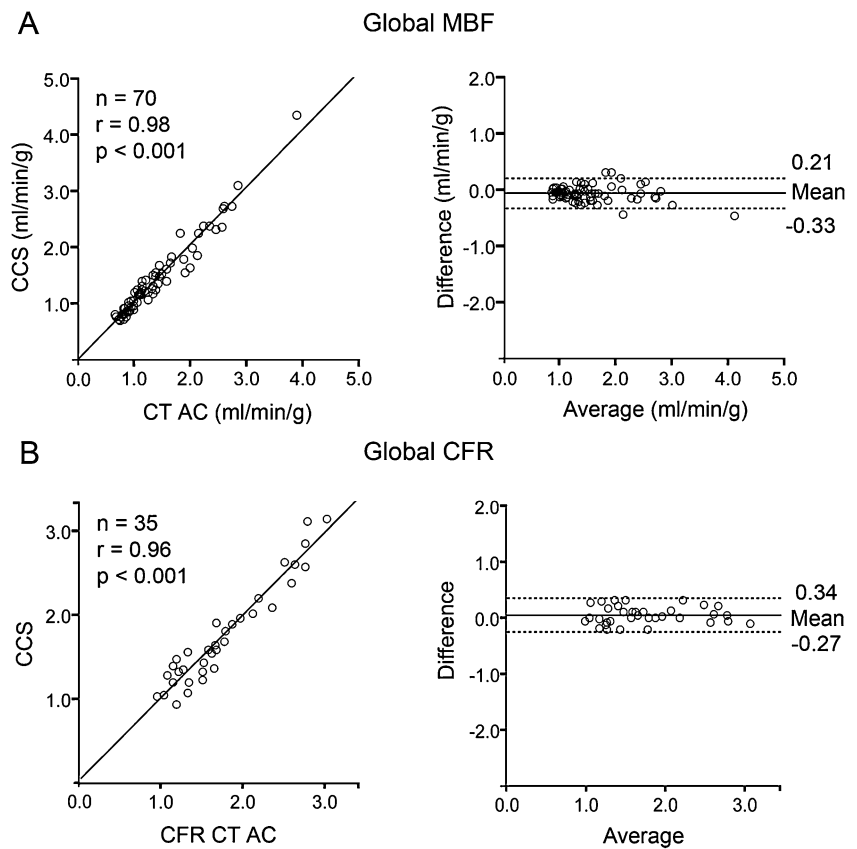
The following issues may be seen as limitations of this study. Scanning parameters and reconstruction algorithms

Table 2 Comparison of global MBF and CFR using CT AC and CCS scans ($n=35$)

	CT AC	CCS	Difference	<i>p</i>	<i>r</i>	<i>p</i>	BA
MBF rest	0.96 ± 0.21	1.02 ± 0.23	-0.06 ± 0.08	ns	0.94	<0.001	−0.21–0.10
MBF stress	1.70 ± 0.66	1.76 ± 0.70	-0.06 ± 0.18	ns	0.97	<0.001	−0.41–0.30
CFR	1.77 ± 0.59	1.75 ± 0.60	0.04 ± 0.16	ns	0.96	<0.001	−0.27–0.34

MBF myocardial blood flow (ml/min per g), *CFR* coronary flow reserve (relative units), *CT AC* computed tomography attenuation correction, *CCS* coronary calcium score scan, *r* correlation coefficient, *BA* Bland-Altman limits of agreement, *ns* non-significant

Fig. 1 a Comparison of global myocardial blood flow (MBF) from coronary calcium scoring (CCS) scans vs computed tomography attenuation correction (CT AC) reveals excellent correlation (*left panel*) and narrow Bland-Altman limits of agreement (*right panel, dashed lines*). **b** Comparison of coronary flow reserve (CFR) from CCS scans vs CT AC reveals excellent correlation (*left panel*) and narrow Bland-Altman limits of agreement (*right panel, dashed lines*)



are optimized specifically for each camera. Thus, the results obtained from our device may not be entirely generalized to other types of PET scanners. In addition, we did not assess whether differences in the extent of coronary calcification may have an impact on the quality of AC and therefore may affect MBF values. Unfortunately, there is no additional independent standard of reference to verify such interference. However, as this would equally apply to both methods of AC it may not have affected the comparability and interchange ability of both methods. Furthermore, we

performed the CCS scan in inspiration following the generally accepted recommendations, although it has been previously reported that CCS in full expiration may be more accurate for correction in the apical myocardium [4]. However, the latter has been reported for SPECT but not for PET scans. In addition, comparison of CCS in inspiration versus expiration was beyond the scope of the present study. Finally, the prognostic value of CCS may be limited in patients with known CAD, although an excellent diagnostic value has been reported for symptomatic patients.

Table 3 Comparison MBF and CFR using CT AC and CCS scans ($n=35$) in the coronary territories

MBF myocardial blood flow (ml/min per g), CFR coronary flow reserve (relative units), CT AC computed tomography attenuation correction, CCS coronary calcium score scan, r correlation coefficient, BA Bland-Altman limits of agreement, LAD left anterior descending artery, CX circumflex artery, RCA right coronary artery, ns non-significant

	CT AC	CCS	Difference	p	r	p	BA
Rest							
LAD	0.94±0.18	1.01±0.21	-0.07±0.11	ns	0.84	<0.001	-0.29–0.14
CX	1.09±0.32	1.13±0.31	-0.04±0.11	ns	0.94	<0.001	-0.25–0.17
RCA	0.90±0.21	0.93±0.24	-0.03±0.09	ns	0.93	<0.001	-0.20–0.14
Stress							
LAD	1.58±0.63	1.68±0.66	-0.08±0.18	ns	0.96	<0.001	-0.44–0.24
CX	1.94±0.73	1.97±0.73	-0.03±0.25	ns	0.94	<0.001	-0.52–0.47
RCA	1.55±0.69	1.58±0.71	-0.03±0.22	ns	0.96	<0.001	-0.44–0.38
CFR							
LAD	1.70±0.58	1.70±0.63	-0.01±0.18	ns	0.96	<0.001	-0.37–0.35
CX	1.90±0.73	1.84±0.67	0.06±0.30	ns	0.91	<0.001	-0.52–0.64
RCA	1.72±0.61	1.71±0.57	0.01±0.20	ns	0.94	<0.001	-0.39–0.41

Conclusion

Use of attenuation maps from CCS scans allows accurate quantitative MBF and CFR assessment with ^{13}N -ammonia PET/CT.

Acknowledgement The study was supported by a grant from the Swiss National Science Foundation (SNSF-professorship grant) and by the ZIHP (Zurich Center for Integrative Human Physiology, University of Zurich, Switzerland). We are grateful to Josephine Trinckauf, Ennio Mueller, Mirjam De Bloeme, Verena Weichselbaumer and Edlira Loga for their excellent technical support.

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